

CHRONIC TOXICITY SUMMARY

BERYLLIUM and BERYLLIUM COMPOUNDS

(beryllium-9; glucinium; glucinum; beryllium metallic)

CAS Registry Number: 7440-41-7

(beryllium oxide; beryllia; beryllium monoxide)

CAS Registry Number: 1304-56-9

(beryllium hydroxide; beryllium hydrate; beryllium dihydroxide)

CAS Registry Number: 13327-32-7

(beryllium sulfate; sulfuric acid; beryllium salt)

CAS Registry Number: 13510-49-1

I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	0.007 mg Be/m³
<i>Critical effect(s)</i>	Beryllium sensitization and chronic beryllium disease in occupationally exposed humans
<i>Hazard index target(s)</i>	Respiratory system; immune system
<i>Oral reference exposure level</i>	0.002 mg/kg-day
<i>Critical effect</i>	Small intestinal lesions in dogs
<i>Hazard index target(s)</i>	Gastrointestinal tract/liver

II. Physical and Chemical Properties Summary (ATSDR, 1993)

	<i>Metallic beryllium</i>	<i>Beryllium oxide</i>	<i>Beryllium hydroxide</i>	<i>Beryllium sulfate</i>
<i>Description</i>	Solid gray, hexagonal structure	White light, amorphous powder	White amorphous powder or crystalline	Colorless tetragonal crystals
<i>Molecular formula</i>	Be	BeO	Be(OH) ₂	BeSO ₄
<i>Molecular weight</i>	9.012 g/mol	25.01 g/mol	43.03 g/mol	105.07 g/mol
<i>Solubility</i>	Insoluble in water			Soluble
<i>Conversion factor</i>	Not applicable			

III. Major Uses and Sources

Beryllium is a metallic element mined as bertrandite and beryl mineral ores. As the lightest structural metal, beryllium is used in the space, aircraft, and nuclear industries in a variety of components including aircraft disc brakes, x-ray transmission windows, vehicle optics, nuclear reactor neutron reflectors, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, and mirrors. In addition to the four species listed, there are many other beryllium-containing compounds, including other salts, ores, and alloys (see, e.g., CRC, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2279 pounds of beryllium (CARB, 2000).

Beryllium alloys, especially the hardest alloy beryllium copper, are used in electrical equipment, precision instruments, springs, valves, non-sparking tools, and in molds for injection-molded plastics for automotive, industrial, and consumer applications. Beryllium oxide is used in high-technology ceramics, electronic heat sinks, electrical insulators, crucibles, thermocouple tubing, and laser structural components. Other beryllium compounds, including the chloride, nitrate, fluoride, and sulfate, are utilized as chemical reagents or generated from the refining of beryllium-containing ores.

Beryllium is naturally emitted into the atmosphere by windblown dusts and volcanic particles. However, the major emission source is the combustion of coal and fuel oil, which releases beryllium-containing particulates and ash. Other beryllium-releasing industrial processes include ore processing, metal fabrication, beryllium oxide production, and municipal waste incineration (ATSDR, 1993). Beryllium also occurs in tobacco smoke (0-0.0005 µg/cigarette) (Smith *et al.*, 1997).

IV. Effects of Human Exposure

The respiratory tract is the major target organ system in humans following the inhalation of beryllium. The common symptoms of chronic beryllium disease (CBD) include shortness of breath upon exertion, weight loss, cough, fatigue, chest pain, anorexia, and overall weakness. Most studies reporting adverse respiratory effects in humans involve occupational exposure to beryllium. Exposure to soluble beryllium compounds is associated with acute beryllium pneumonitis (Eisenbud *et al.*, 1948). Exposure to either soluble or insoluble beryllium compounds may result in obstructive and restrictive diseases of the lung, called chronic beryllium disease (berylliosis) (Cotes *et al.*, 1983; Johnson, 1983; Infante *et al.*, 1980; Kriebel *et al.*, 1988a; Metzner and Lieben, 1961). The total number of beryllium-related disease cases has declined since the adoption of industrial standards (Eisenbud and Lisson, 1983; ATSDR, 1993).

Historically, beryllium pneumonitis has been associated with occupational concentrations over 0.1 mg Be/m³, primarily as beryllium sulfate or beryllium fluoride (Eisenbud *et al.*, 1948). The atmospheric concentrations related to chronic beryllium disease have been more difficult to define, in part due to the lack of individual exposure estimates, especially in the studies derived from the berylliosis case registries (Infante *et al.*, 1980; Lieben and Metzner, 1959). However,

Infante and associates (1980) reported significantly increased mortality due to non-neoplastic respiratory disease in beryllium-exposed workers, and noted one case of chronic berylliosis in a worker following seven years exposure to $\leq 2 \mu\text{g Be/m}^3$. In a 30-year follow-up study of 146 beryllium-exposed workers, Cotes *et al.* (1983) identified seven cases of chronic beryllium related disease. All the cases were exposed to beryllium oxide or hydroxide, but in a wide range of retrospectively estimated doses (over 3000 samples from 1952 to 1960). The estimated average daily exposure did not exceed $2 \mu\text{g Be/m}^3$ for the ten site/process classifications, but 318 samples did exceed $2 \mu\text{g Be/m}^3$ (and 20 samples were greater than $25 \mu\text{g Be/m}^3$). No atmospheric samples were available after 1963, even though the exposure occurred through 1973. The LOAEL for occupationally induced berylliosis observed in this study was estimated from uncertain exposure data to be less than $2 \mu\text{g Be/m}^3$.

One cross-sectional study (Kriebel *et al.*, 1988a; Kriebel *et al.*, 1988b) estimated beryllium exposure levels for 309 workers originally surveyed in 1977, with a median duration of exposure of 17 years (range 2 to 39 years). Historic plant levels were estimated to be as high as $100 \mu\text{g Be/m}^3$, and, even as late as 1975, some job classifications exceeded $10 \mu\text{g Be/m}^3$. The workers' median cumulative exposure was $65 \mu\text{g Be/m}^3\text{-year}$ (range 0.1 to $4400 \mu\text{g Be/m}^3\text{-years}$); the median lifetime exposure estimate was $4.3 \mu\text{g Be/m}^3$ (range 0.01 to $150 \mu\text{g Be/m}^3$). Spirometric measurement of pulmonary function, chest x-rays, and arterial blood gas measurements were collected. Decrements in lung function, as defined by forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), were associated with cumulative exposure up to 20 years prior to the health survey, even in workers with no radiographic abnormalities. Differences in alveolar-arterial oxygen gradient were associated with cumulative exposure in the 10 years prior to the study. These endpoints give a LOAEL of $39 \mu\text{g Be/m}^3\text{-years}$ (geometric mean cumulative exposure) for decrements in pulmonary function and changes in arterial blood gases.

Non-occupational beryllium-related chronic disease has been reported in individuals residing in the vicinity of beryllium manufacturing industries (Eisenbud *et al.*, 1949; Metzner and Lieben, 1961). An early cross-sectional study (Eisenbud *et al.*, 1949) described 11 cases of non-occupational berylliosis after x-ray and clinical examination of approximately 10,000 residents near a beryllium fabrication facility in Lorain, Ohio. Ten of the cases resided within 3/4 mile of the plant (up to 7 years duration), and five cases resided within 1/4 mile. The authors estimated a 1% disease incidence within 1/4 mile (500 individuals). Atmospheric sampling in 1947 identified an average level of $0.2 \mu\text{g Be/m}^3$ at 1/4 mile decreasing to $0 \mu\text{g Be/m}^3$ at 10 miles, but samples varied up to 100 fold over the 10 week sampling period. Utilizing current and historical exposure estimates based on discharge, process, inventory, and building design changes, this study estimated a chronic LOAEL in the range of 0.01 to $0.1 \mu\text{g Be/m}^3$ for continuous exposure to beryllium compounds, based on the development of chronic berylliosis.

Metzner and Lieben (1961) also reported 26 cases of chronic berylliosis in a population of approximately 100,000, living within 7 miles of a refining and alloy fabrication plant (duration 6 to 19 years). Neighborhood exposure assessment conducted over 14 months during 1958 and 1959 identified a mean level of $0.0155 \mu\text{g Be/m}^3$, with 10% of the samples registering over $0.03 \mu\text{g Be/m}^3$. Limited measurements conducted earlier at the site were higher (1.0 to $1.8 \mu\text{g Be/m}^3$ in 1953 and 0.91 to $1.4 \mu\text{g Be/m}^3$ in 1954).

Chronic beryllium disease appears to involve a cell-mediated immune response, especially granulomatous reactions found in the lungs of sensitive individuals. Humans exposed to beryllium compounds have demonstrated increased T-cell activity (*in vitro*) and histological abnormalities of the lymph nodes (Cullen *et al.*, 1987; Johnson, 1983). Johnson (1983) described granuloma of lymph nodes and chronic interstitial pneumonitis in a small number of beryllium metal handling machinists (LOAEL = $4.6 \mu\text{g Be/m}^3$). A second study identified granulomatous lung lesions, scarred lung tissue, and breathing difficulties in workers from a precious metal refining facility exposed to a mixture of beryllium and other metals (Cullen *et al.*, 1987). Also, altered proliferative responses of lymphocytes obtained by bronchoalveolar lavage indicated increased T-cell activity *in vitro*. Cullen *et al.* (1987) reported a mean exposure level of $1.2 \mu\text{g Be/m}^3$ (range = $0.22 - 43 \mu\text{g/m}^3$). USEPA (1998) and ATSDR (2000) considered $0.52 \mu\text{g Be/m}^3$ to be the LOAEL for CBD from this study since this was the average concentration in the furnace area where 4 of the 5 CBD cases worked.

Sensitization to beryllium, as measured by the beryllium lymphocyte proliferation test (BeLPT), can occur in the absence of chronic beryllium disease (Kreiss *et al.*, 1989). The authors hoped that the identification of sensitized individuals without disease might prevent clinical disease, presumably by removing the individuals from exposure to beryllium. Some beryllium-sensitized individuals progress to having clinical disease (Newman *et al.*, 1992). Data obtained from a four-year survey conducted at beryllium-copper alloy manufacturing factories in Japan (Yoshida *et al.*, 1997) indicated that the T cells of workers continuously exposed to more than $0.01 \mu\text{g Be/m}^3$ were activated and that the cell-mediated immune (CMI) response was promoted. The BeLPT in workers exposed to less than $0.01 \mu\text{g Be/m}^3$ was unaffected.

Genetic influences on development of CBD have been identified. CBD is associated with the allelic substitution of glutamic acid for lysine at position 69 in the HLA-DPB1 protein (Richiardi *et al.*, 1993). Up to 97% of CBD patients may have the Glu69 marker, but only 30-45% of beryllium-exposed, unaffected individuals carry the same marker. Because CBD occurs in only 1-6% of exposed workers, Glu69 is not likely to be the only genetic factor influencing the development of CBD. Changes in other sequences of the HLA-DPB1 gene and in the copy number of Glu69 are also involved (Wang *et al.*, 1999).

The Rocky Flats Environmental Technology Site in Colorado is part of the U.S. Department of Energy nuclear weapons complex. Operations using Be began in 1953, Be production operations began in 1957, and the first case of CBD was diagnosed in a machinist in 1984. Exposures could have occurred during foundry operations, casting, shearing, rolling, cutting, welding, machining, sanding, polishing, assembly, and chemical analysis operations. Since 1991, 29 cases of CBD and 76-78 cases of beryllium sensitization have been identified (Stange *et al.*, 1996). Several cases appear to have had only minimal Be exposure, since the employees were in administrative functions, not primary beryllium operations. Personal air monitoring devices used over a period of 4 years showed a breathing zone level of $1.04 \mu\text{g Be/m}^3$. ATSDR (2000) considered $1.04 \mu\text{g Be/m}^3$ to be the LOAEL for this study. A recent case-control study of workers at Rocky Flats (Viet *et al.*, 2000) suggested that exposures of workers to lower Be levels might lower the future incidence of CBD, but not necessarily the incidence of sensitivity to Be.

Kreiss *et al.* (1996) investigated the prevalence of beryllium sensitization in relation to work process and beryllium exposure measurements in a beryllia ceramics plant that had operated since 1980. In 1992 they interviewed 136 employees (97.8% of the workforce), ascertained beryllium sensitization with the beryllium lymphocyte proliferation blood test (BeLPT), and reviewed industrial hygiene measurements. Eight employees were beryllium-sensitized (5.9%); six of the eight had granulomatous disease based on transbronchial lung biopsy. Machinists had a Be sensitization rate of 14.3% compared to 1.2% among other employees. Machining operations (drilling, dicing, centerless grinding, and/or surface grinding) had significantly higher general area and breathing zone measurements than other work processes during the time in which most beryllium-sensitized cases had started machining. Daily weighted average estimates of exposure for machining processes also exceeded estimates for other work processes in that time period (median daily weighted average = $0.9 \mu\text{g}/\text{m}^3$). Daily weighted averages for the machining process accounted for the majority of exceedances of the $2.0 \mu\text{g}/\text{m}^3$ OSHA Permissible Exposure Limit (PEL); 8.1% of machining daily weighted averages were above the PEL. The LOAEL from this study was $0.55 \mu\text{g}/\text{m}^3$, the median exposure of the sensitized workers.

The facility was again surveyed in 1998 after some attempts were made to lower exposure to beryllium (Henneberger *et al.*, 2001). The investigators separated the workers into 77 long-term workers hired before the 1992 screening and 74 short-term workers hired after 1992. Among 20 short-term workers exposed to the lowest mean Be level (0.05 to $0.19 \mu\text{g}/\text{m}^3$), two showed Be sensitivity by the BeLPT test. Thus a fraction of workers appears to be exquisitely sensitive to beryllium.

Based on a review of this and other occupational studies Wambach and Tuggle (2000) have suggested that the workplace standard of $2 \mu\text{g}/\text{m}^3$ be lowered to $0.1 \mu\text{g}/\text{m}^3$. Some workers might still be sensitized to beryllium at this level (Yoshida *et al.*, 1997).

V. Effects of Animal Exposure

Three chronic studies, two in rats (Vorwald and Reeves, 1959; Reeves *et al.*, 1967) and one in guinea pigs (Reeves *et al.*, 1970), observed adverse inflammatory and proliferative respiratory changes following inhalation exposure to beryllium compounds. Vorwald and Reeves (1959) observed inflamed lungs and fibrosis in rats exposed to $0.006 \text{ mg Be}/\text{m}^3$ (as BeO) for an unspecified duration. A later study exposed Sprague-Dawley CD rats for 72 weeks (7 hr/d, 5 d/wk) to $34.25 \mu\text{g Be}/\text{m}^3$ from BeSO₄ (Reeves *et al.*, 1967). Gross and histological changes observed in exposed versus unexposed rats included increased lung weight, inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis, and proliferative responses within the alveoli (LOAEL = $34.25 \mu\text{g Be}/\text{m}^3$). Guinea pigs were exposed to 0, 3.7, 15.4, or $29.3 \mu\text{g Be}/\text{m}^3$ (from the sulfate) for 6 hours/day, 5 days/week for up to 1 year (Reeves *et al.*, 1970). Respiratory alterations observed in the beryllium-exposed groups included increased tracheobronchial lymph node and lung wet weights, interstitial pneumonitis, and granulomatous lesions. These adverse respiratory effects were observed in all the beryllium dosed groups and indicated a chronic inhalation LOAEL of $3.7 \mu\text{g Be}/\text{m}^3$.

Wagner *et al.* (1969) exposed monkeys, rats, and hamsters to 0.21 and 0.62 mg Be/m³ as fumes from bertrandite or beryl ore, respectively, for 6 hours/day, 5 days/week for up to 17 months. Exposed animals displayed severe effects, including (1) bronchial lymphocytic infiltrates, abscesses, consolidated lobes, and granulomatous lesions after exposure to 0.21 mg Be/m³ from bertrandite ore, and (2) inflamed lungs, fibrosis, and granuloma after exposure to 0.62 mg Be/m³ from beryl ore. Lung inflammation was observed in the exposed monkeys, and a few granulomatous lung lesions were observed in the hamsters after similar exposure conditions (up to 23 months).

Immunological effects have been observed in a few subchronic studies (Schepers, 1964; Schepers *et al.*, 1957; Stiefel *et al.*, 1980). Schepers (1964) exposed monkeys (*Macacus mullata*) to three soluble forms of beryllium (BeF₂, BeSO₄, BeHPO₄) daily for 6 hours/day over 7 to 30 days. Increased lung weight, inflammation, emphysema, and fibrosis of the lung were observed after 17 days at 0.198 mg Be/m³ (as BeSO₄). Histological examination found pleuritis, congestion, emphysema, consolidation, and edema of the lung. Immunological effects were seen as hyperplasia of the lymph nodes typical of immune activation after 7 to 18 days exposure to either 0.198 or 0.184 mg Be/m³ as the sulfate or fluoride. A subchronic inhalation study reported immunological effects as increased, beryllium-specific stimulation of T-lymphocytes *in vitro* from Wistar rats and guinea pigs exposed daily (6 hours/day) over 10 weeks (LOAEL = 0.5 mg/m³) (Stiefel *et al.*, 1980). However, a subchronic inhalation study in Wistar and Sherman rats (Schepers *et al.*, 1957) observed multiple lung alterations including granulomas (LOAEL = 35 µg Be/m³) but did not find any accompanying immunological effects after 30 days discontinuous exposure (5-6 d/wk, 4-8 hr/d) to beryllium fumes from BeSO₄.

VI. Derivation of Chronic Reference Exposure Levels

Derivation of Inhalation Reference Exposure Level

<i>Key study</i>	Kreiss <i>et al.</i> , 1996
<i>Study population</i>	8 beryllium-sensitized workers among 136 employees in a beryllia ceramics plant
<i>Exposure method</i>	Workplace
<i>Critical effects</i>	Beryllium sensitization (chronic beryllium disease)
<i>LOAEL</i>	0.55 µg/m ³ (median exposure of sensitized workers)
<i>NOAEL</i>	Not observed
<i>Exposure continuity</i>	Workplace
<i>Average experimental exposure</i>	0.2 µg/m ³ for LOAEL group (0.55 x 10/20 x 5/7)
<i>Human equivalent concentration</i>	0.2 µg/m ³
<i>Exposure duration</i>	6.1 years (5 mo – 10 yr)
<i>LOAEL uncertainty factor</i>	10 (low incidence but serious, irreversible chronic disease)
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3 (sensitized may not be only sensitive subpopulation) (see below)
<i>Cumulative uncertainty factor</i>	30
<i>Inhalation chronic REL</i>	0.007 µg/m ³
<i>Supportive study</i>	Eisenbud <i>et al.</i> (1949)
<i>Study population</i>	Approximately 10,000 individuals within 2 miles of a beryllium manufacturing plant
<i>Exposure method</i>	Environmental exposure
<i>Critical effects</i>	Pulmonary berylliosis in 11 residents
<i>LOAEL</i>	0.03 µg/m ³ (geometric mean of range of measured exposures associated with berylliosis of 0.01 to 0.1 µg/m ³)
<i>NOAEL</i>	Not observed
<i>Exposure continuity</i>	Continuous
<i>Average exposure</i>	Estimated to be approximately 0.3 µg/m ³ (historical exposures estimated to be 10-fold higher than measured values) for LOAEL group
<i>Human equivalent concentration</i>	0.3 µg/m ³ for LOAEL group
<i>Exposure duration</i>	Up to 7 years
<i>LOAEL uncertainty factor</i>	10
<i>Subchronic uncertainty factor</i>	3
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	100
<i>Inhalation chronic REL</i>	0.003 µg/m ³

U.S. EPA (1998) developed an RfC of $0.02 \mu\text{g}/\text{m}^3$ based on beryllium sensitization and progression to chronic beryllium disease (CBD) identified by Kreiss *et al.* (1996). The Kreiss *et al.* (1996) occupational exposure study identified a LOAEL for beryllium sensitization in workers of $0.55 \mu\text{g}/\text{m}^3$ (median of average exposure concentrations of the 8 Be sensitized workers). The Eisenbud *et al.* (1949) study, which U.S. EPA used as a co-principal study and which in U.S. EPA's opinion used relatively insensitive screening methods, suggested a NOAEL of $0.01\text{-}0.1 \mu\text{g}/\text{m}^3$ in community residents living near a beryllium plant. U.S. EPA used the LOAEL from the Kreiss *et al.* (1996) study for the operational derivation of the RfC, because the screening method used in the Eisenbud *et al.* (1949) study was considered to be less sensitive than the method used in the Kreiss *et al.* (1996) study. The LOAEL was time adjusted to $0.2 \mu\text{g}/\text{m}^3$, then a total UF of 10 was used to obtain the RfC of $0.02 \mu\text{g}/\text{m}^3$. The UF of 10 was comprised of a UF of 3 to account for the sensitive nature of the subclinical endpoint (beryllium sensitization) and a database UF of 3 to account for the poor quality of exposure monitoring in the Kreiss *et al.* and Eisenbud *et al.* studies. Poor exposure monitoring was also a problem in other epidemiology studies that assessed the incidence of beryllium sensitization. The U.S. EPA did not explicitly apply a LOAEL to NOAEL uncertainty factor. Thus implicitly the factor is 1.

OEHHA prefers to use the methodology for assignment of UFs, which is described in OEHHA (2000) and used in our derivation of the REL for beryllium, including use of a LOAEL to NOAEL Uncertainty Factor of 10. Since chronic beryllium disease (CBD) is serious, chronic, disabling, usually irreversible, and often fatal (Newman *et al.*, 1997), it is difficult to justify use of a LOAEL to NOAEL factor of only 3. OEHHA has not used database deficiency UFs since the criteria for use of such factors are not well specified by U.S. EPA. The people who get CBD are likely that part of the population who are by nature more sensitive to beryllium, for example those with the human leukocyte antigen (HLA) class II marker HLA-DP Glu69 (Richeldi *et al.*, 1993; Saltini *et al.*, 1998). Although it is likely that the effects are seen in a "sensitive subpopulation," OEHHA applied an intraspecies uncertainty factor (UF_H). OEHHA used an intermediate UF_H of 3, since 1) there may be other population factors involved in being sensitive, such as immature lungs, and 2) all the diseased were initially healthy adult workers.

For comparison the LOAEL from guinea pigs of $3.7 \mu\text{g Be}/\text{m}^3$ (Reeves *et al.*, 1970) is equivalent to a continuous exposure of $0.66 \mu\text{g}/\text{m}^3$. Division by UFs of 10 for intraspecies, 10 for interspecies (since HEC adjustments are not available yet for guinea pigs), and 10 for use of a LOAEL results in a REL of $0.0007 \mu\text{g}/\text{m}^3$.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the inhalation chronic REL for beryllium is the use of human data from persons occupationally exposed. The major uncertainties are the lack of a NOAEL observation in the key study, the lack of long-term exposure data, the difficulty of estimating exposures, and the lack of chronic exposure data.

VIII. Potential for Differential Impacts on Children's Health

No evidence to support a differential effect of beryllium on infants or children was found in the literature. However, children have developed beryllium disease from metal brought home on the parents' work clothes and by living near a facility using beryllium. Unfortunately the number of children and their ages were not published (Eisenbud *et al.*, 1948).

Derivation of Chronic Oral Reference Exposure Level

In addition to being inhaled, airborne beryllium can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level for beryllium is also required for conducting Air Toxics Hot Spots risk assessments.

<i>Study</i>	Morgareidge <i>et al.</i> , 1976
<i>Study population</i>	Male and female dogs (5/sex/group)
<i>Exposure method</i>	Diet containing 0, 1, 5, 50 or 500 ppm Be as beryllium sulfate tetrahydrate
<i>Critical effects</i>	Small intestinal lesions
<i>LOAEL</i>	500 ppm
<i>NOAEL</i>	50 ppm (1.2 mg/kg bw-day)
<i>Exposure continuity</i>	Continuous
<i>Exposure duration</i>	Up to 3 years, 4 months
<i>Average experimental exposure</i>	1.2 mg/kg bw-day (males, 1.1; females, 1.3)
<i>BMD₀₅</i>	0.244 mg/kg-day
<i>LOAEL uncertainty factor</i>	Not needed in BMD approach
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	10
<i>Intraspecies factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Oral reference exposure level</i>	0.002 mg/kg-day

Morgareidge *et al.* (1976) conducted a long-term feeding study in which beagle dogs (aged 8 to 12 mo) were fed diets (for 1 h per day) containing 0, 5, 50, or 500 ppm Be for 172 weeks. The 500 ppm group was terminated at 33 weeks because of overt signs of toxicity, and an additional group was added to the study and fed a diet containing 1 ppm Be (for 143 weeks). The 1, 5, 50, and 500 ppm concentrations corresponded to doses of 0.023, 0.12, 1.1, and 12.2 mg/kg-day for males and 0.029, 0.15, 1.3, and 17.4 mg/kg-day for females. All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine and to a lesser extent in the stomach and large intestine, and were considered treatment related. All animals with stomach or large intestinal lesions also had lesions in the small intestine, except for one animal (whose stomach lesions were very localized and not very severe). Lesions in the small intestine (4/5 males and 5/5 females) were considered to be treatment-related and included desquamation of the epithelium, edema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis and thinning/atrophy of the epithelium, and ulceration. High-dose animals also showed

moderate to marked erythroid hypoplasia of the bone marrow, which the authors also considered treatment related. (Bile stasis and vasculitis in the liver, acute inflammation in the lymph nodes, and kidney occurring in these animals was attributed to a likely systemic bacterial invasion through the damaged intestinal mucosa.) In the 50 ppm group, one female dog, which died after 70 weeks of treatment, showed gastrointestinal lesions, which were less severe, but occurred in the same locations and appeared to be the same types of lesions as those in dogs administered 500 ppm. The observation that beryllium is poorly absorbed by the gastrointestinal tract (Owen, 1990; ATSDR, 2000) probably explains why lesions were not seen outside the gastrointestinal tract. In addition the predominance of lesions in the small intestine may have been partly due to precipitation of beryllium phosphate there due to the slightly alkaline pH (Reeves, 1965). Thus 500 ppm was a LOAEL and 50 ppm was a NOAEL (statistically) for gastrointestinal lesions.

USEPA used the same study to derive its RfD of 0.002 mg/kg-day. The U.S. EPA stated its confidence in the RfD as: study - medium; database – low to medium, and RfD - low to medium. USEPA used a BD₁₀ approach and included a database UF of 3. OEHHA used a BD₀₅ approach (specifically a Weibull model in the USEPA's BMDS software) and did not include a database UF since the criteria for use of modifying factors such as this are not well specified by U.S. EPA. However, the final value for the oral chronic REL was the same as the USEPA's RfD.

This RfD and the oral REL are limited to soluble beryllium salts. Data on the teratogenicity or reproductive effects of beryllium are limited. Beryllium has been reported to produce terata and increased mortality in chick embryos.

When assessing the health effects of beryllium, its carcinogenicity must also be assessed.

IX. References

ATSDR. 1993. Agency for Toxic Substances and Disease Registry. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Beryllium. TP-92/04. Atlanta, GA: ATSDR. April 1993.

ATSDR. 2000. Agency for Toxic Substances and Disease Registry. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Beryllium (update). Draft for Public Comment. Atlanta, GA: ATSDR. September 2000.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

Cotes JE, Gilson JC, McKerrow CB, and Oldham P. 1983. A long-term follow-up of workers exposed to beryllium. Br. J. Ind. Med. 40:13-21.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Cullen M, Kominsky J, Rossman M, Cherniack M, Rankin J, Balmes J, Kern J, Daniele R, Palmer L, Naegel G, McManus K, and Cruz R. 1987. Chronic beryllium disease in a precious metal refinery. Clinical epidemiologic and immunologic evidence for continuing risk from exposure to low level beryllium fume. *Am. Rev. Respir. Dis.* 135:201-208.

Eisenbud M, and Lisson J. 1983. Epidemiological aspects of beryllium-induced nonmalignant lung disease: A 30 year update. *J. Occup. Med.* 25:196-202.

Eisenbud M, Berghout CF, and Steadman L. 1948. Environmental studies in plants and laboratories using beryllium: the acute disease. *J. Ind. Hyg. Toxicol.* 30:282-285.

Eisenbud M, Wanta R, Dustan C, Steadman L, Harris W, and Wolf B. 1949. Nonoccupational berylliosis. *J. Ind. Hyg. Toxicol.* 31:282-294.

Henneberger PK, Cumro D, Deubner DD, Kent MS, McCawley M and Kreiss K. 2001. Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant. *Int. Arch. Occup. Environ. Health.* 74(3):167-176.

Infante PF, Wagoner JK, and Sprince NL. 1980. Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the beryllium case registry. *Environ. Res.* 21:35-43.

Johnson NR. 1983. Beryllium disease among workers in a spacecraft-manufacturing plant - California. *MMWR.* 32:419-425.

Kreiss K, Newman LS, Mroz MM, and Campbell PA. 1989. Screening blood test identifies subclinical beryllium disease. *J. Occup. Med.* 31(7):603-608.

Kreiss K, Mroz MM, Newman LS, Martyny J, and Zhen B. 1996. Machining risk of beryllium disease and sensitization with median exposures below 2 micrograms/m³. *Am. J. Ind. Med.* 30(1):16-25.

Kriebel D, Sprince NL, Eisen EA, Greaves I, Feldman H and Greene R. 1988a. Beryllium exposure and pulmonary function: A cross sectional study of beryllium workers. *Br. J. Ind. Med.* 45:167-173.

Kriebel D, Sprince NL, Eisen EA, and Greaves I. 1988b. Pulmonary function in beryllium workers: Assessment of exposure. *Br. J. Ind. Med.* 45:83-92.

Lieben J, and Metzner F. 1959. Epidemiological findings associated with beryllium extraction. *Am. Ind. Hyg. Assoc.* 20:494-499.

Metzner F, and Lieben J. 1961. Respiratory disease associated with beryllium disease - A case study. *J. Occup. Med.* 3:341-345.

Morgareidge K, Cox GE and Gallo MA. (1976) Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America, Alcan Research & Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc.

Newman LS, Mroz MM, Schumacher B, Daniloff E, and Kreiss K. 1992. Beryllium sensitization precedes chronic beryllium disease. *Am. Rev. Resp. Dis. (Suppl)* 145:A324.

Newman LS, Lloyd J, and Daniloff E. 1996. The natural history of beryllium sensitization and chronic beryllium disease. *Environ. Health Perspect.* 104S(5):937-943.

OEHHA. 2000. Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part III. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Available on-line at <http://www.oehha.ca.gov>

Owen BA. 1990. Literature-derived absorption coefficients for 39 chemicals via oral and inhalation routes of exposure. *Regul. Toxicol. Pharmacol.* 11(3):237-252.

Reeves AL. 1965. The absorption of beryllium from the gastrointestinal tract. *Arch. Environ. Health.* 11(2):209-214.

Reeves AL, Deitch D, and Vorwald AJ. 1967. Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. *Cancer Res.* 27:439-443.

Reeves AL, Swanborg RH, Busby EK, and Krivanek ND. 1970. In: *Target Organ Toxicology Series: Immunotoxicology and Immunopharmacology*. Dean J, Luster M, Munson A, and Amos H, eds. New York, NY: Raven Press, Inc. pp. 441-456.

Richeldi L, Sorrentino R, and Saltini C. 1993. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. *Science* 262(5131):242-244.

Saltini C, Amicosante M, Franchi A, Lombardi G and Richeldi L. 1998. Immunogenetic basis of environmental lung disease: lessons from the berylliosis model. *Eur Respir J.* 12(6):1463-75.

Schepers GW. 1964. The biological action of beryllium: Reaction of the monkey to inhaled aerosols. *Ind. Med. Surg.* 33:1-16.

Schepers GW, Durkhan TM, Delahunt AB, and Creedon FT. 1957. The biological action of inhaled beryllium sulfate. A preliminary chronic toxicity study in rats. *AMA Arch. Ind. Health* 15:32-58.

Schroeder HA, and Mitchner M. 1975. Life-term studies in rats: Effects of aluminum, barium, beryllium and tungsten. *J. Nutr.* 105:421-427.

Smith CJ, Livingston SD and Doolittle DJ. 1997. An international literature survey of "IARC Group I carcinogens" reported in mainstream cigarette smoke. *Food Chem. Toxicol.* 35(10-11):1107-1130.

Stange AW, Hilmas DE, and Furman FJ. 1996. Possible health risks from low level exposure to beryllium. *Toxicology* 111(1-3):213-224.

Stiefel T, Schulze K, Zorn H, and Toelg G. 1980. Toxicokinetic and toxicodynamic studies of beryllium. *Arch. Toxicol.* 45:81-92.

U.S. Environmental Protection Agency. 1998. Integrated Risk Information System (IRIS) Database. Available online at <http://www.epa.gov/iris>

Viet SM, Torma-Krajewski J, and Rogers J. 2000. Chronic beryllium disease and beryllium sensitization at Rocky Flats: a case-control study. *AIHAJ.* 61(2):244-254.

Vorwald A, and Reeves A. 1959. Pathologic changes induced by beryllium compounds. *Arch. Indust. Health* 19:190-199.

Wagner W, Groth D, Holtz J, Madden G, and Stokinger H. 1969. Comparative chronic inhalation toxicity of beryllium ores bertrandite and beryl, with production of pulmonary tumors by beryl. *Toxicol. Appl. Pharmacol.* 15:10-29.

Wambach PF, and Tuggle RM. 2000. Development of an eight-hour occupational exposure limit for beryllium. *Appl. Occup. Environ. Hyg.* 15(7):581-587

Wang Z, White PS, Petrovic M, Tatum OL, Newman LS, Maier LA, and Marrone BL. 1999. Differential susceptibilities to chronic beryllium disease contributed by different Glu69 HLA-DPB1 and -DPA1 alleles. *J. Immunol.* 163(3):1647-1653.

Yoshida T, Shima S, Nagaoka K, Taniwaki H, Wada A, Kurita H, and Morita K. 1997. A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. *Ind. Health* 35(3):374-379.